THE IMPACT OF PRE-EXPOSURE PROPHYLAXIS ON MEN WHO HAVE SEX WITH MEN IN CAMEROON: A MODELING STUDY

by

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Abstract

Men who have sex with men (MSM) have been consistently burdened by human immunodeficiency virus (HIV) at higher rates than adults in the general population. Cameroon has a large MSM population throughout its major cities. Though PrEP has been shown to reduce infections in MSM populations, it has yet to be introduced in Cameroon. This study uses a mathematical model to simulate population level HIV transmission in Cameroon among MSM. PrEP is incorporated into the model to assess the effects to HIV prevalence and prevented infections. The model simulated an HIV prevalence of 16.4%, annual diagnoses of 946 infections per 100,000 MSM and antiretroviral (ART) coverage of 74.2%. PrEP as a standalone intervention at 10% and 20% intervention resulted in HIV prevalence decreasing by 3.8% and 5.4% over a 20-year intervention, respectively. A 10% increase in HIV testing combined with a PrEP intervention at 10% initiation resulted in prevalence being reduced even further, by 5.0% to 11.4%. This same intervention reduced the percentage of infected individuals that were unaware of their status from 15.6% to 6.7%. The interventions with the largest effect in reducing prevalence were the combination of PrEP and increased HIV testing. PrEP was beneficial to reducing prevalence and preventing infections even at low initiation and coverage levels.

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Introduction

The Human Immunodeficiency Virus (HIV) pandemic continues to expand among men who have sex with men (MSM), despite declining in most other populations[1-3]. Studies from high-income countries suggest that MSM are at greater risk of infection, while MSM in low and middle income countries may face high levels of stigma and may have limited access to interventions[4,5]. Using pre-exposure prophylaxis (PrEP) as a means of preventing HIV has been shown to prevent new infections in MSM[6]. Mathematical model studies can provide valuable insight into the possible impacts of interventions.

HIV-negative individuals can use antiretroviral therapy (ART) to protect themselves against getting infected with HIV, called PrEP. PrEP has been tested in many forms, a vaginal microbicide gel comprised of 1% tenofovir was tested among a cohort of women in South Africa. It prevented 39% of infections overall and over 50% in individuals with high adherence. Use of a dapivirine vaginal ring has been used more recently with a decrease in incidence of 37% compared to placebo[7]. Though one trial using oral PrEP failed to provide any efficacy in a cohort of women in South Africa and Kenya, it remains the only trial to date that did not protect against infection[8]. The Pre-Exposure Prophylaxis Initiative (iPrEx) tested oral PrEP as a standalone intervention among MSM and transgender women and found a 44% reduction in incidence[6]. Oral PrEP has proven safety and efficacy in MSM populations.

In large part due to these prevention resources, there has been an increase in optimism surrounding the control of the HIV pandemic, though MSM epidemics continue to grow. HIV prevalence among MSM remains high in many regions of the world such as the Caribbean, where prevalence is roughly 25%. HIV prevalence among MSM is around 15-18% in Sub-Saharan Africa, North America, Central and South America, and South and Southeast Asia[9]. This burden is brought on by social and biologic factors that leaves MSM epidemics continuously growing[9]. HIV infection spreads quickly through networks of undiagnosed and untreated MSM. A study in the UK found that in large MSM networks, 20% of HIV transmission intervals were found to occur within 6 months[10]. This is, in part, due

to the high HIV transmission probability of condomless receptive anal intercourse with a serodiscordant and viremic sexual partner, which is 11-18 times higher than that of condomless vaginal sex[11,12].

MSM in Sub-Saharan Africa have been persistently ignored [13]. Many factors have converged to leave MSM neglected and at higher risk of infection than the general population in Africa. Early reports of male-to-male HIV transmission were originally overlooked and disregarded[14]. Knowledge and access to HIV prevention materials continues to be a problem in some regions[13]. High-income settings often see interventions and treatment much faster than low and middle income countries[4,15]. ART was not scaled up until between 2004 and 2007 in several African countries, such as Kenya, Malawi, Uganda and Tanzania, nearly a decade after the first treatments (protease inhibitors) were introduced in the United States in 1995[16,17]. A systematic review found that MSM in Africa were 3.8 times as likely to be living with HIV than reproductive-aged men[5,18]. The stigma associated with being MSM also creates an environment wherein indiviudals do not disclose their sexual orientation to healthcare providers. A study found that only 24% of MSM disclosed their MSM status to healthcare professionals in Batswana, while only 9% disclosed their status in Malawi[19]. This inhibits these individuals from seeking necessary prevention and treatment services. This is brought on by criminalization of homosexual behavior which hinders the ability to seek services and preventive measures[20]. The high risk of transmission combined with a large disease burden and high levels of stigma creates a situation in which standalone interventions are not enough to curb the epidemic[15].

In Cameroon, there are an estimated 20,118 to 28,598 MSM living in the major urban centers, while 66,842 MSM are estimated to be living in the country[21,22]. One study found that only a quarter of MSM had revealed their sexual orientation to a health care professional[23]. HIV prevalence is estimated to be around 21% throughout the country while the prevalence among the general population in Cameroon is estimated to be 4.3%. Approximately 10% of the MSM population in urban centers were unaware of their HIV status. Behavioral and biologic interventions exist in Cameroon but PrEP has not been implemented[23].

While clinical trials have shown that PrEP can reduce incidence, modeling the outcomes of a prep intervention allows for interpretations of the effects at the population level. One modeling study of female sex workers in Botswana, Kenya, and India demonstrated that PrEP would have a much greater impact on the number of prevented infections in Botswana and Kenya compared to India[24]. Another study modeling PrEP among MSM and transgender women in Peru found that low levels of PrEP coverage among high priority individuals could be cost-effective but would still require a large financial backing to implement[25].

While previous models have focused on PrEP use in heterosexual couples, combination intervention among MSM in South Africa, or PrEP on the MSM population in Peru, they have not addressed the dynamics of HIV in Cameroon among MSM[25-27]. This model focuses specifically on transmission characteristics of HIV among MSM in Cameroon and the impacts of varied PrEP interventions on a population level.

Methods

Model

The mathematical model used here has been previously described[28]. The model is intended to simulate HIV transmission among MSM in Cameroon with the ability to incorporate the impact of PrEP intervention. This is a deterministic, compartmental model with 5 compartments; susceptible to infection (X), susceptible while on PrEP (X_{PrEP}), infected but not diagnosed (I_{ND}), infected and diagnosed but not on treatment (I_D), and infected, diagnosed and on treatment (I_{DT}). The model is represented in figure 1.

The movement through compartments is determined by the rates at which people become infected, find out they are positive through testing, initiation or stop treatment, and initiate PrEP. These are represented by the force of infection (λ), force of infection while on PrEP (λ_{PrEP}), rate of PrEP initiation (σ), rate of HIV testing (ψ), rate of ART initiation (κ), and rate of ART dropout (κ_{DT}), Entry and exit rate not due to HIV (μ), exit rate while infected (μ_{HIV}), and exit rate while infected and on treatment

(μ_{HIV_T}). Both of the force of infection parameters (λ and λ_{PrEP}) are based on two activity levels using the number of partners, the number of sex acts per partnership, and the per act transmission probability, outlined in table 1. One key assumption made was that individuals on PrEP who became infected were aware of their HIV status within one year and therefore moved straight to the diagnosed compartment (I_D). Another assumption made was that this population did not actively participate in serosorting and therefore exhibited proportional mixing.

Parameters

The model is parameterized by data collected in the 2016 Integrated Biological and Behavioral Surveillance (IBBS) survey among female sex workers and men who have sex with men in Cameroon (hereafter referred to as: IBBS 2016). This survey is a cross-sectional study conducted among female sex workers and MSM throughout five major urban centers in Cameroon. Participants were recruited through respondent driven sampling and trained interviewers gathered data through a behavioral questionnaire and serological testing. For this model of HIV transmission in MSM, we only used the MSM data from this IBBS 2016. When data was not available from this study we used data from similar areas throughout Central and Eastern Africa, summarized in Tables 1 and 2.

In order to accurately parameterize the model, we used ranges from the IBBS 2016 survey to fit five of the model parameters and the three outcome parameters, the rest of the parameters were fit with point estimates for efficiency through IBBS 2016 or similar literature. All model parameters are outlined in table 1. The outcome parameters were based on prevalence, rate of new diagnoses (per 100,000 MSM) and ART coverage over the past 10 years, and are outlined in Table 2.

Calibration

Calibration of this model was done using Latin Hypercube Sampling (LH) for the five model parameters with ranges in order to optimize the results from this model. Using LH, each of the five parameters was split into ten equal sized bins. Every possible bin combination was used to create a

sample of simulated epidemics, for a total of 10^5 simulations. For every simulated epidemic, the value within each bin was sampled randomly within the ranges of that bin. The model was run for 200 years to allow it to converge. If the results of the epidemic fell within the ranges of all three outcome parameters; prevalence, new diagnoses, and ART coverage, outlined in table 2, they were kept for further analysis. Of the simulated epidemics that fit the outcome parameters, maximum likelihood was tested of each outcome parameter. The maximum likelihood values for each outcome parameter were combined in even weights for each simulated epidemic to form a cumulative maximum likelihood value. The parameter values from the simulated epidemic with the overall highest cumulative maximum likelihood was used to parameterize the original compartmental model.

Intervention

After calibration, the original deterministic model was run. First, it was run without any PrEP intervention to create a baseline from which the effects of PrEP could be drawn. The effects were assessed by the change in prevalence and percent of prevented infections. These were based on **1)** different PrEP initiation rates over varied timeframes, **2)** different PrEP coverage levels over a 20-year intervention , **3)** the additional benefit of increased HIV testing due to PrEP intervention and **4)** the effects of intervention on the proportion of individuals that are infected but undiagnosed. Data calculations for the model and outcome parameters were done using STATA 14.2 (College Station, Texas). The model was run and calibrated using MATLAB R2017b (9.3.0.713579) maci64. Some figures were created using RStudio version 1.1.419.

Results

Calibration

The model was first calibrated over a 100-year timeframe but failed to converge so it was then run over 200 years which reached equilibrium. From the initial 10^5 epidemic simulations, 4681

simulations hit, wherein all three outcome parameters were satisfied. Figure 2 is a graphical depiction of the final epidemic values after 200 years of running the model. Maximum likelihood analyses resulted the combination of prevalence, annual diagnoses and ART coverage likelihood estimates with the cumulative maximum likelihood of 0.9936 (Figure 3). The model parameters corresponding to the maximum likelihood of the outcome parameters are outlined in table 3. The maximum likelihood model resulted in a prevalence of 16.4%, annual diagnoses of 946 per 100,000 MSM and an ART coverage of 74.2%, after 200 years.

Intervention

After running the model for 200 years, a standalone PrEP intervention was added to study the effects. PrEP initiation of 5% and 10% of susceptible individuals per year resulted in an estimated prevalence of 14.1% and 12.6%, respectively, after 20 years of intervention compared to a baseline of 16.4% (Figure 4). These same initiation rates correspond to 13.8% and 22.6% of infections prevented over the 20-year intervention (Figure 5). When increased to a 50-year intervention, the prevalence decreases to 11.1% and 8.4% for 5% and 10% PrEP initiation rates, while prevented cases over the same time period increases to 32.6 and 48.8%, respectively (Figure 5).

If PrEP interventions were implemented with a goal of 25%, 50% or 75% coverage at the end of a 20-year intervention, the initiation rates per year would have to be 5.5%, 14.2% and 33.1%, respectively. Prevalence as a result of these programs would be 13.95%, 11.85%, and 9.95% after 20 years (Figure 6). The percent of infections prevented due to PrEP in these interventions would be 14.95%, 27.76% and 39.32%. Based on the percent of infections prevented per 1% initiation rate, the outcomes were 2.69%, 1.95% and 1.88% cases prevented per unit of initiation for the 25%, 50% and 75% coverage interventions, respectively (Figure 7).

A PrEP initiation rate of 10% per year would result in a prevalence of 12.6% after 20-years, but if the HIV testing rate per year increased by 10% over the intervention, the prevalence would further reduce to 11.4% (Figure 10). Similarly, a 20% initiation rate over the same duration would change the

prevalence from 11.0% to 9.9% with an increase in HIV testing rate of 10% (Figure 10). The increase in testing decreases the prevalence between year 0 and 5, but the effect size would remain relatively constant at a level of just over 1% for the duration of intervention.

With the benefits of additional testing, the proportion of undiagnosed cases per total infected would drop. After a 20-year intervention with an initiation rate of 5% per year, the total number of infections would drop by 22.6% (Figure 8). Over the same intervention, the proportion of undiagnosed infections out of the total infections would drop from 15.6% at the start of the intervention to 9.7%. Combined with a 10% increase in testing, the percentage of undiagnosed cases would drop to 6.7% over the same timeframe. A 20% initiation rate with a 10% increase in testing would change the proportion of unaware individuals from 15.6% to 4.2% over 20 years (Figure 8).

Discussion

The model converges after 200 years and PrEP intervention, at different lengths of time and levels of initiation, were added to the model with the possibility of incorporating an increased HIV testing rate. The results from the PrEP intervention demonstrate that prevented infections would increase and HIV prevalence would decrease with an increase in the initiation rate of PrEP. The greatest benefits would come from the highest levels of PrEP initiation, but the highest benefit, measured in infections prevented, to resource ratio would come at low levels of initiation and coverage. Increased testing, as a result of the PrEP intervention, would result in a further increases to prevented cases and decreases in prevalence. PrEP implementation would reduce the percentage of infected individuals that are undiagnosed.

The model demonstrates the benefits to prevalence and prevented infections from a range of standalone PrEP interventions. But as Initiation rate of PrEP increases, the benefit decreases. A study from South Korea showed that PrEP can reduce incidence of HIV among MSM as an independent intervention. This study also assessed any reduction in benefit from PrEP due to risk compensation and

found that PrEP was still beneficial[29]. In this model, PrEP was able to reduce prevalence even at low levels of initiation.

PrEP was scaled to reach different levels of coverage at the conclusion of a 20-year intervention, 25%, 50% and 75% coverage. The maximum cases averted per 1% initiation rate were found at the 25% coverage intervention. Challenges, such as knowledge and attitude towards PrEP, may act as challenges in attempting to implement large PrEP interventions, making effective but modest interventions very appealing. In 2014, MSM were interviewed about attitudes towards PrEP during a pride fair in Portugal. 59% of MSM had not heard about PrEP, but of those that had, 57% responded that they were likely to use PrEP if made available[30]. Similarly, in a review looking at studies between 2009 and 2016, the overall estimate of acceptability of oral PrEP was 56%[20]. While positive perceptions of PrEP are likely to increase among MSM as exposure increases, it takes less resources to create programs that involve fewer individuals. If PrEP is beneficial at low levels, it may be optimal to use small initiation rates and to scale up as demand increases, therefore saving resources while still preventing infections.

The standalone intervention from the model prevented cases and reduced incidence of HIV, but a standalone intervention is not expected to end transmission of this infection. Increased HIV testing should accompany any PrEP intervention since testing would likely be a prerequisite to starting PrEP for individuals that want to enroll[31]. This model demonstrated that a 10% increase in testing could have large effects on the prevalence and could further prevent cases when acting in collaboration with a PrEP intervention (Figures 9 and 10). A modeling study among MSM in South Africa showed that reducing the number of individuals that didn't recieve an HIV test each year from 1/3 of the population to 1/6 resulted in around a 5% increase in prevented infections[27]. 10% is a modest increase in HIV testing and the benefits would only be greater if testing increased more than 10%. But, decreasing HIV prevalence and increasing the number of prevented infection are not the only impacts that increased testing would have on the results of the model.

This PrEP intervention, and the increase in testing, would impact the percentage of individuals that are infected with HIV but unaware (Figure 8). Individuals who are infected but unaware of their

infection remain a crucial component to spreading HIV. Studies have shown that those unaware of their HIV status have significant risks of onward HIV transmission[32]. Individuals aware of their status have also been shown to be less likely to engage in condomless sex[33-35]. One of the suggestions by the CDC in 2005 to reduce HIV transmission was to increase testing in order to reduce the proportion of unaware infections[36].

Limitations

There were several limitations in this study. First, Cameroon is a large country with several large cities with variable HIV transmission and prevalence, it may not be ideal to generalize the HIV transmission estimates to the entire countries when each city could have its own transmission characteristics. Second, there are limited data within Cameroon and some of the model parameters were estimated from settings within the same region of West and Central Africa. This led to limited precision in the outcome parameters, though they were based on data within the country.

Conclusions

This model shows that PrEP has the ability to reduce prevalence and prevent infections among MSM in Cameroon even at low levels of initiation and coverage. Based on this model, the combination intervention of PrEP and increased HIV testing was able to, not only, reduce the prevalence of HIV, but also, decrease the percentage that are infected but unaware of their infection. Reducing HIV transmission is a a slow process, but PrEP has a place among a suite of interventions that should be implemented. PrEP has the ability to limit HIV transmission in an area that has often been overlooked, among a population that is heavily and disproportionately burdened.

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Model			
Parameter	**Symbol**	**Range or value**	**Source**
Proportion of high activity group	N_H/N_L	[0.05, 0.24]	IBBS 2016, [37]
Ratio of number of partnerships high-activity group to low-activity group	C_H/C_L	[9, 27]	IBBS 2016
Transmission risk, receptive acts	$ß_r$	[0.002, 0.025]	[38]
HIV testing rate (per year)	ψ	[0.32, 0.64]	IBBS 2016
ART initiation rate (per year)	κ	[0.57, 0.74]	IBBS 2016
Number of partners, low activity group	C_L	4	IBBS 2016
condom use proportion, negative-negative	pc_{11}	0.77	IBBS 2016
condom use proportion, positive-negative	pc_{12}	0.83	IBBS 2016
Proportion of viral suppression among ART users	T_{ART}	0.88	IBBS 2016
Transmission risk, insertive acts	$ß_i$	0.0011	[38]
ART dropout rate	κ_D	0.2	IBBS 2016
Annual number of sex acts per partnership	Nsa	23	IBBS 2016
Condom efficacy	d_{condom}	80%	[39]
PrEP efficacy	Ω	44%	[6]
Entry/exit rate	μ	0.026	IBBS 2016, [40]
Exit rate due to HIV mortality	μ_{HIV}	0.076	[16]
Exit rate due to HIV mortality while on ART	μ_{HIV_T}	0.031	[16]

Table 1. **Model parameters**. The first five parameters: proportion of high activity group, ratio of number of partnerships of high-activity group to the low-activity group, transmission risk of receptive acts, HIV testing rate per year and ART initiation rate per year, all used ranges in the calibration. The latter parameters used point estimates based on the sources.

Parameter	Range	Source
Prevalence	4-45%	IBBS 2016
Diagnoses (Annual diagnoses per 100,000 MSM)	23-1880	IBBS 2016, [22]
ART coverage	69-92%	IBBS 2016, [23]

Table 2. **Outcome parameters.** Simulated epidemics within these bounds were kept for maximum likelihood calculations. Diagnoses were calculated from the number of individuals who tested positive in a given year divided by the estimated MSM population in that area. The low end was created when 1 individual became HIV positive in Douala where the estimated MSM population is 4,438. The upper end of the range came from Kribi, where 5 individuals were infected in a given year, where the MSM population is estimated at 266 [22].

Table 3

Parameter	Symbol	Range	Maximum likelihood estimate values
Proportion of high activity group	N_H/N_L	[5, 24]	0.06
Ratio of number of partnerships	C_H/C_L	[9, 27]	11.5
Transmission risk, receptive acts	$ß_r$	[0.002, 0.025]	0.003
HIV testing rate	ψ	[0.32, 0.64]	0.37
ART initiation rate	κ	[0.57, 0.74]	0.74

Table 3 **Model parameter results**. Based on the cumulative maximum likelihood based on the Latin Hypercube Sampling. The MLE column were the point estimates used in the model with PrEP intervention.

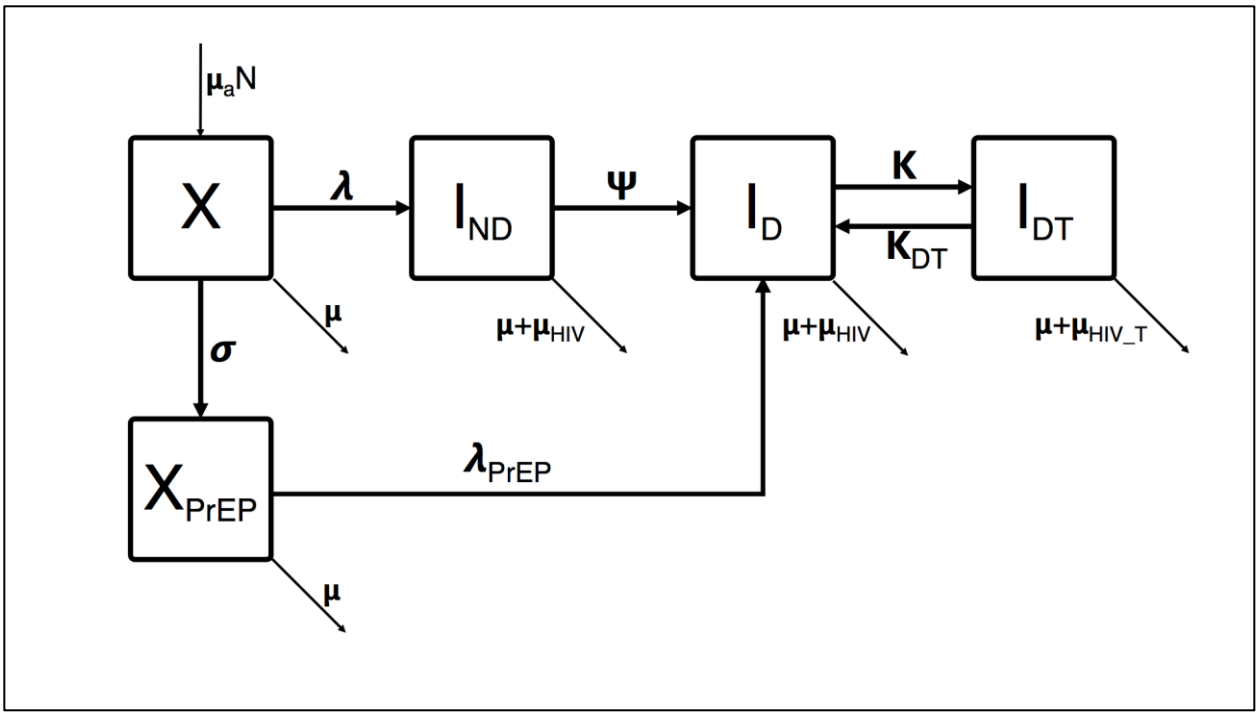

Figure 1. **Model figure**. The compartments are: susceptible to infection (X), susceptible while on PrEP (X_{PrEP}), infected but not diagnosed (I_{ND}), infected and diagnosed but not on treatment (I_D), and infected, diagnosed and on treatment (I_{DT}). The rates of exchange between compartments are: the force of infection (λ), force of infection while on PrEP (λ_{PrEP}), rate of PrEP initiation (σ), rate of HIV testing (ψ), rate of ART initiation (κ), and rate of ART dropout (κ_{DT}), Entry and exit rate not due to HIV (μ), exit rate while infected (μ_{HIV}), and exit rate while infected and on treatment (μ_{HIV_T}). Individuals who are on PrEP (X_{PrEP}) who become infected become aware of their HIV status within one year and therefore move to the diagnosed (I_D) compartment.

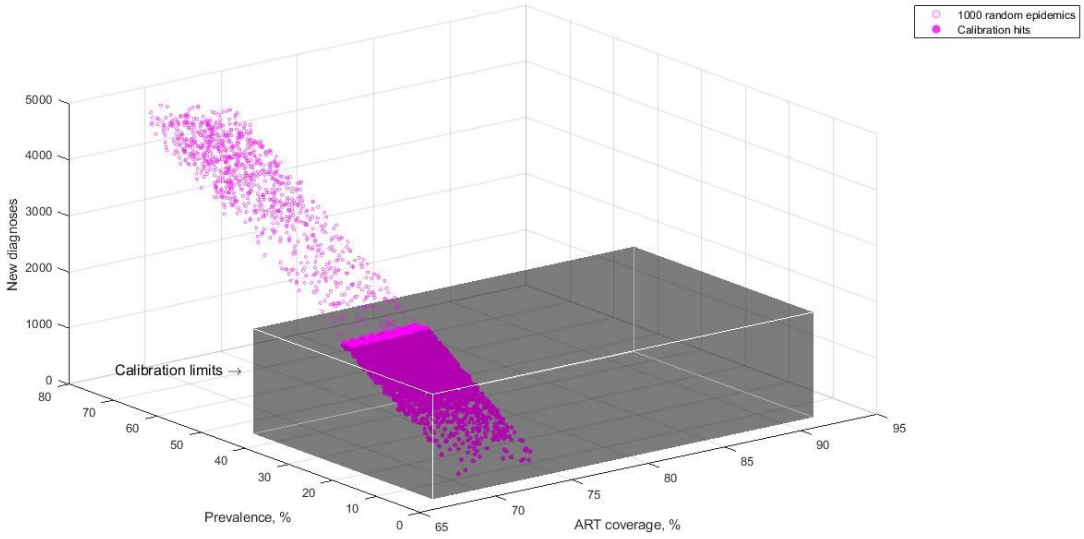

Figure 2. **All simulations.** Depicts a random sampling of the outcome parameters from the simulations that did not satisfy all three outcome parameters (open circles) with all simulations that did satisfy all outcome parameters (closed circles). The gray rectangular prism depicts the range in which satisfied all three outcome parameters.

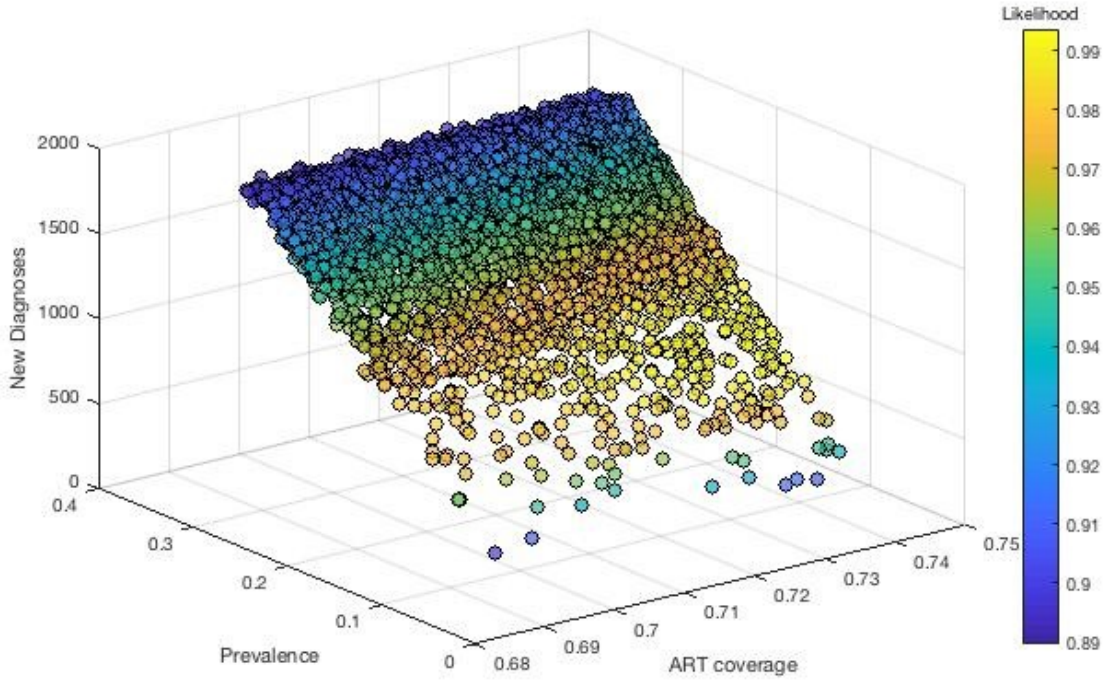

Figure 3. **Maximum likelihood of hits.** Depicts the simulations of epidemics that fit our outcome parameters. They were given a cumulative maximum likelihood which is the color of the points.

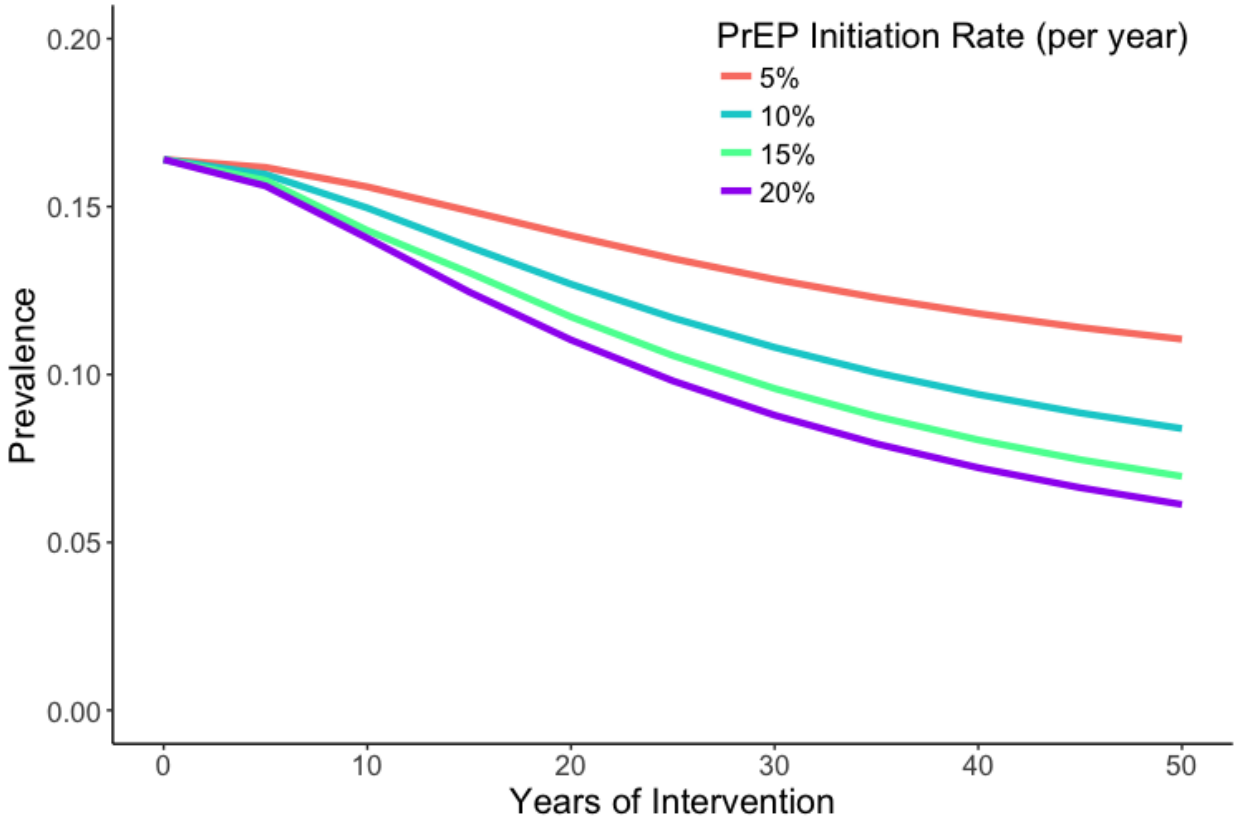

Figure 4. **Prevalence over varied standalone interventions.** Prevalence based on a varied intervention length at different PrEP initiation rates.

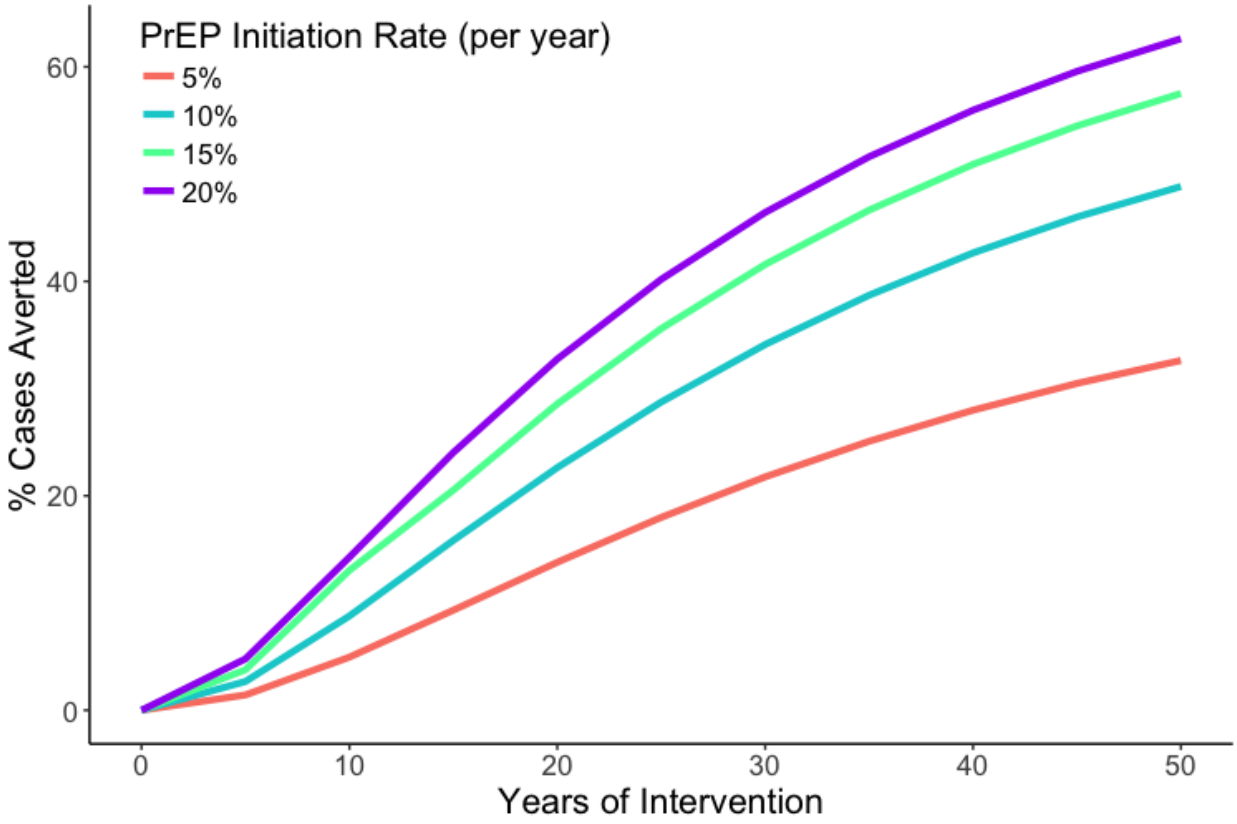

Figure 5. **Percent cases averted over varied standalone PrEP interventions.** Percent of cases averted from different PrEP interventions combining PrEP initiation rate and different lengths of intervention.

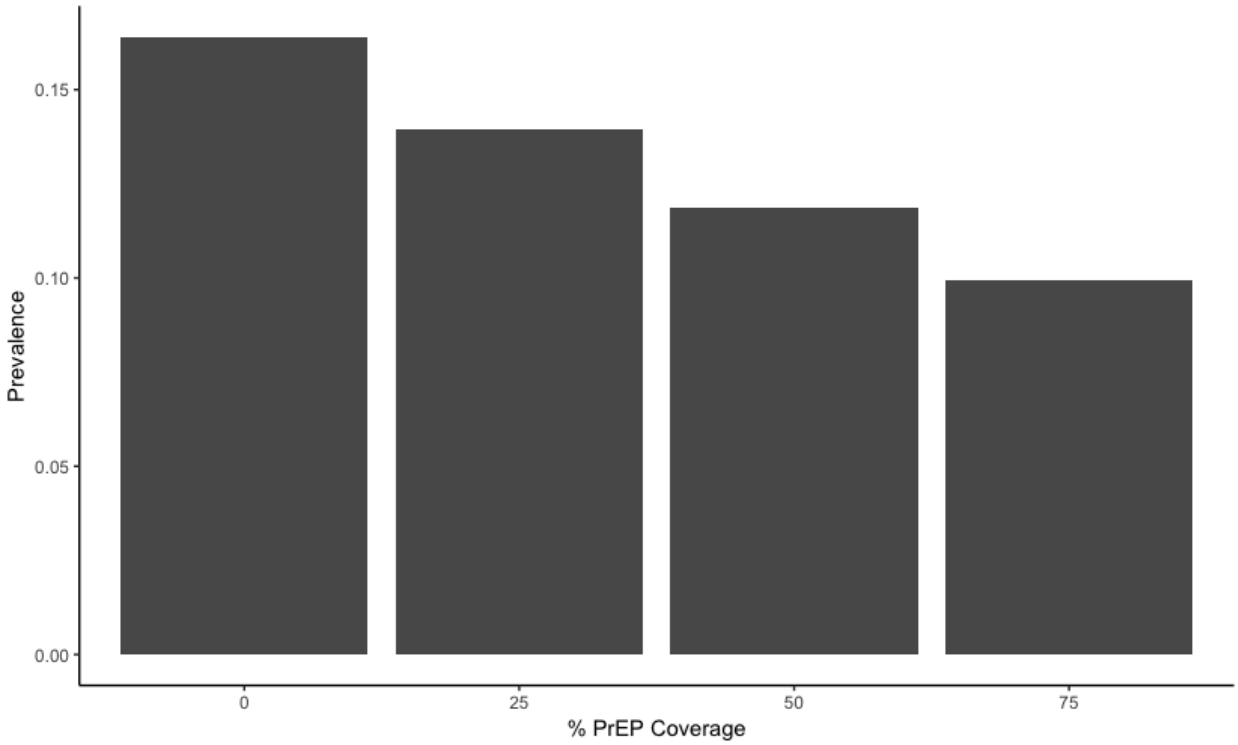

Figure 6. **Prevalence from PrEP coverage interventions.** Prevalence at the end of a 20-year intervention that sought coverage of 25%, 50%, and 75% at the end of the intervention.

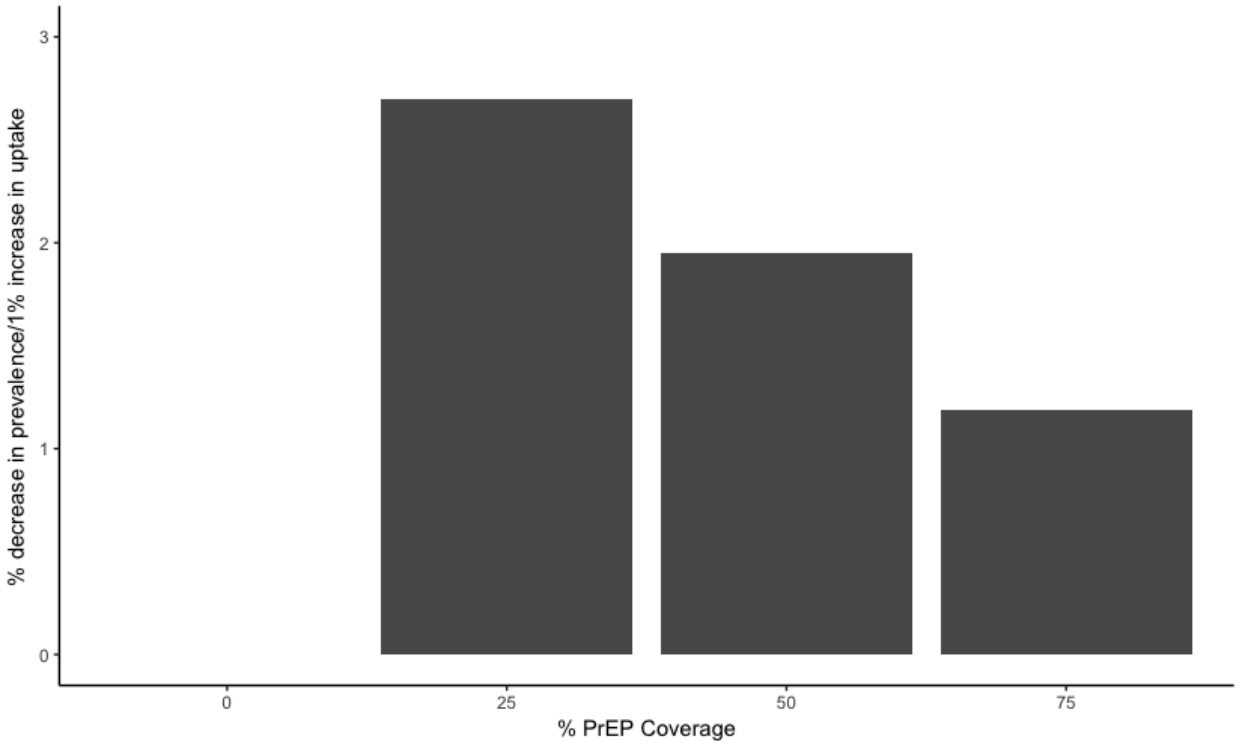

Figure 7. **Change per effort for PrEP coverage interventions.** Change in prevalence per effort, measured as percent initiation rate of intervention in order to reach desired coverage. Initiation rates were 5.5%, 14.2% and 33.1% corresponding to 25%, 50%, and 75% coverage, respectively.

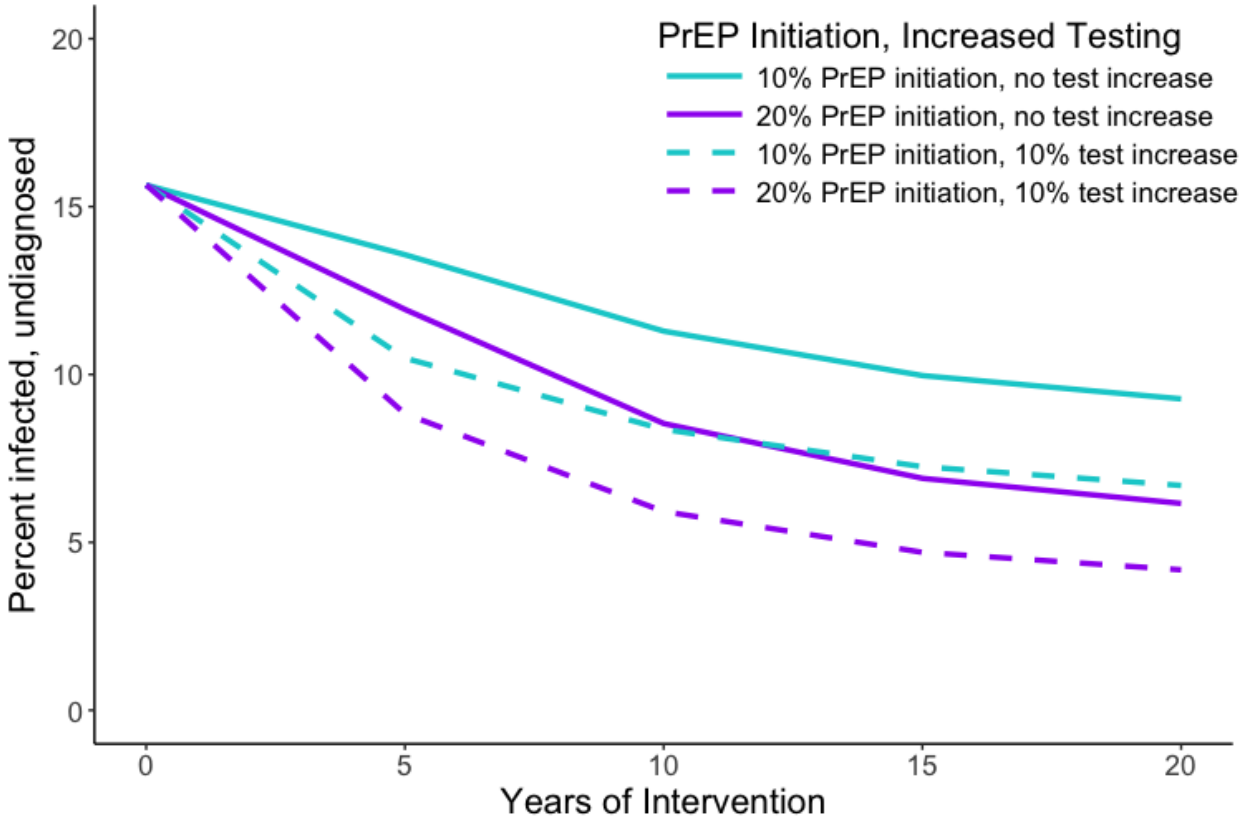

Figure 8. **Percent infected and unaware.** The percent infected who are undiagnosed out of total infected over two different initiation rates combined with increased testing.

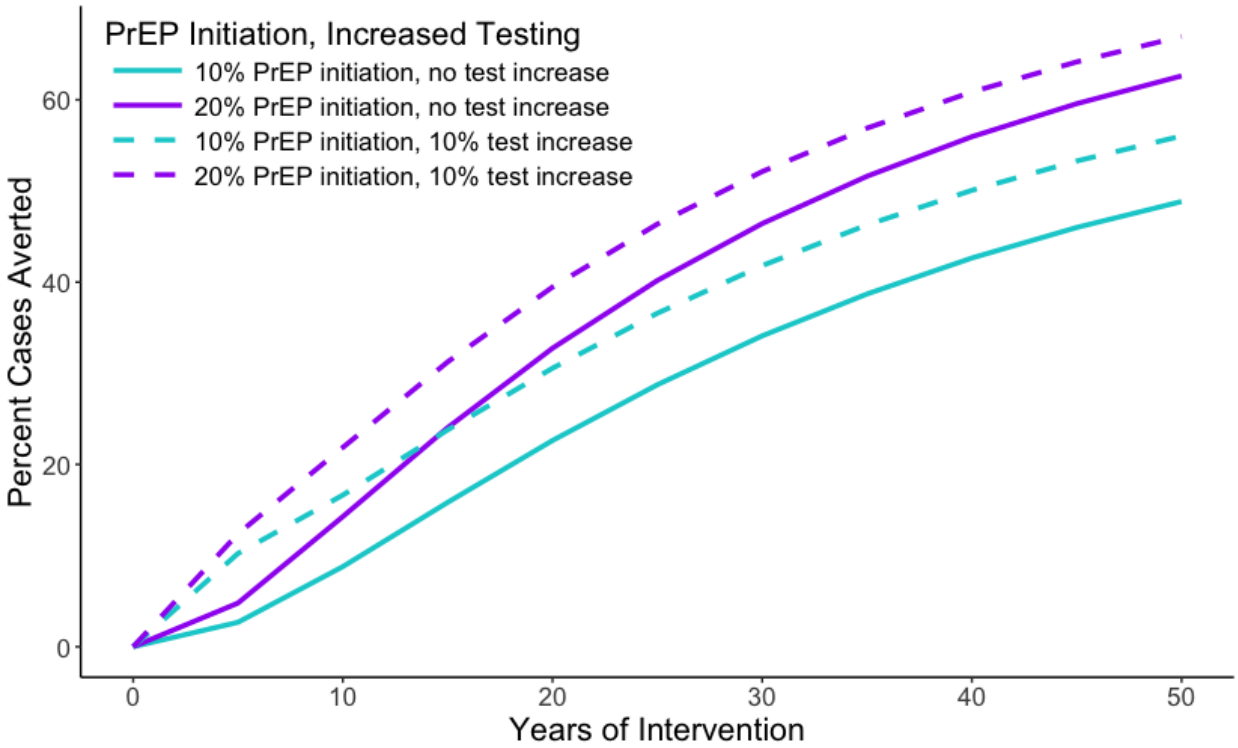

Figure 9. **Prevented infections based on combination PrEP and test intervention.** Percent of cases prevented based on initiation rate and an increase in HIV testing rate of 10% over different lengths of intervention.

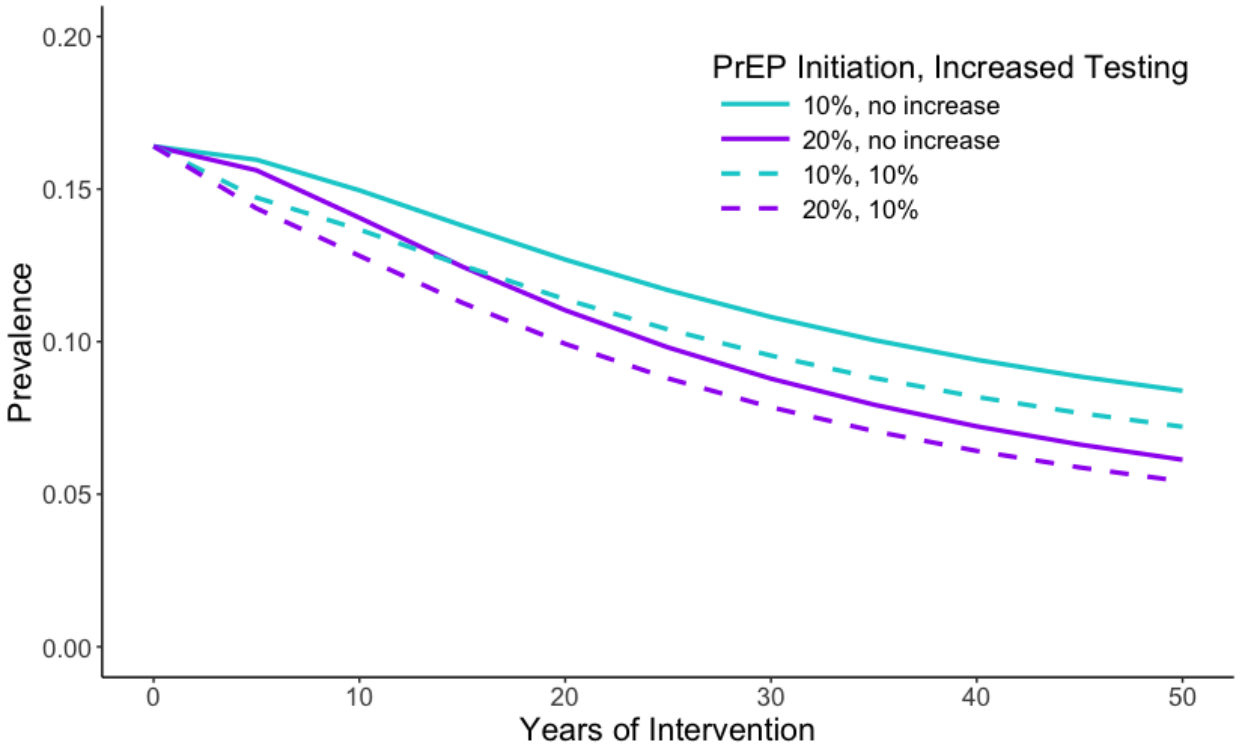

Figure 10. **Prevalence based on combination PrEP and test intervention.** Change in prevalence as an artifact of PrEP initiation rate and a 10% increase in HIV testing rate over different lengths of intervention.

Biographical Sketch

Owen was born in Philadelphia, PA in 1991. He attended Northeastern University from 2010-2014 where he studied Behavioral Neuroscience and Marine Biology and graduated with a Bachelors of Science. He enrolled in the Three Seas Program as during his senior year and traveled to Nahant, MA, Bocas del Toro, Panama and San Juan, WA to study marine science and learn how to conduct research. After graduation, he then moved to Florida to work as a laboratory technician studying the health and predation of oysters and collecting data for the Florida-Georgia water wars supreme court case.

In 2016, Owen began his Masters of Science in Epidemiology at Johns Hopkins Bloomberg School of Public Health. He studied infectious disease and worked as a research assistant for a systematic review on key populations in HIV research that led to his interest in key populatins and the motivation for this thesis.

In his free time, Owen enjoys SCUBA diving and baking brownies from the box. On rainy days he can be found curled up under a fluffy blanket with a cup of hot chocolate and a good book.